REVIEW ARTICLE

Asthma in pregnancy: a review

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Summary: Asthma is one of the most common medical conditions in women of childbearing age. There are now data to show that asthma is not a benign condition with respect to maternal and fetal health. Despite this there are several problems encountered in the management of such women. There is a tendency to cease or reduce optimal asthma treatments because pregnant women and/or their clinicians may believe they pose a risk to the fetus. There is also a lack of clinician awareness of the complications of asthma in pregnancy.

Keywords: maternal-fetal medicine, high-risk pregnancy, drugs (medication), allergy, asthma, pregnancy

In the following review, we will illustrate why rather than arbitrarily reducing or ceasing therapy, it is much more important to ensure the optimal treatment of asthma to maintain maternal health and normal fetal growth and maturation. The mainstay of maternal monitoring has been spirometry and peak flow measurement. More recently measurement of expired nitric oxide is showing promise as a new monitoring modality.

BACKGROUND

Asthma is one of the most common chronic medical conditions in pregnancy[1–3] and the second most common reason for administration of prescription drugs in pregnancy.[4] In Australia the incidence of asthma in the community is one of the highest in the world at 12–13%, much higher than figures quoted for the rest of the globe (3.7% to 8.4%).[5–10] Unfortunately, the incidence in pregnancy mirrors that found in the community but for many clinicians this condition 'flies under the radar' and women may not receive optimal care throughout their pregnancy.[11]

The effects of pregnancy on asthma symptoms

The conventional diagnosis of asthma is made by demonstrating airway obstruction on spirometry that is at least partially reversible (>12% increase in forced expiratory volume in the first second of expiration (FEV_1) after bronchodilator therapy) in a patient with typical symptoms of wheezing, chest tightness, cough and associated shortness of breath. Conventional wisdom is that asthma in pregnancy follows the 'one-third rule', i.e. one third will improve, one third will deteriorate and one third will remain unchanged. More recent reports have challenged this with the percentage being noted to deteriorate to the point of exacerbation during pregnancy depending on the initial severity of the asthma.[8,12,13] Amongst pregnant women diagnosed with mild asthma there is an 8% risk of deterioration resulting in exacerbation compared with a 47% and 65% risk of deterioration resulting in exacerbation in women diagnosed with moderate or severe asthma respectively.[14] While some women will improve in the first trimester, deterioration is mostly noted in the late second trimester with only infrequent problems occurring in late pregnancy and in labour.

There are a number of factors that may particularly trigger asthma in pregnancy. These include viral infections,[15] active smoking[16,17] and non-adherence to inhaled corticosteroid medication.[15] With respect to viral infections there are some data to support the hypothesis of reduced cell-mediated immunity during pregnancy. This was particularly so with seasonal and H1N1 influenza[8,18] and women are advised to undertake influenza vaccination during pregnancy.[19]

The effect of asthma on placental function

The placenta is a key regulator of fetal maturation and its function may be compromised by maternal asthma. The effect of asthma on placental function has been reported by several authors. Stereological assessment of placental morphology shows that fetoplacental growth is compromised in pregnancies complicated by asthma.[20] Placentae collected after delivery from women with asthma show significant reduction in Corticotrophin Releasing Hormone (CRH)-induced vasodilatation in moderate and severe asthmatics. CRH is a potent vasodilator produced by the placenta and acts via the nitric oxide pathway. In women with asthma, umbilical artery Doppler ultrasound assessment of blood flow has shown a reduction in resistance at 18 weeks gestation which had disappeared by 30 weeks gestation.[21] These resistance changes were significantly different from normal non-asthmatic controls. The concern is that this difference in early pregnancy may not be beneficial to placental vascular development as hyperoxia in early pregnancy has been identified as an inhibitor of terminal placental villous development and angiogenesis.[22] Also noted were changes in vasoconstrictor responses to KCl and prostaglandin $F_{2\alpha}$ in this group of pregnant asthmatics

compared with non-asthmatic controls. Notably the above changes were more exaggerated in asthmatic women who were smokers. These results show a number of alterations in the placental vascular responses in women with moderate and severe asthma that could be associated with adverse perinatal outcomes.

Reduction of the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) has been correlated with non-use of inhaled corticosteroids (ICS) in pregnancy and accompanied a 25% reduction in birthweights of the fetuses of these women, which was a significant reduction compared to birthweights among women without asthma. 11β-HSD2 acts as a barrier in the placenta by metabolising cortisol (which is inhibitory to fetal growth) to its inactive metabolite cortisone protecting the fetus from excess maternal cortisol. In this study, there was an increase in neonatal cortisol levels, accompanied by a trend to increased placental CRH and reduced fetal oestriol concentrations among neonates whose mothers had asthma which was not treated with inhaled corticosteroids.[23] Others have reported that plasma from pregnant women significantly increases the production of IL-6 ($P<0.001$) and secreted RANTES ($P<0.01$) in human bronchial smooth muscle cells which may be one mechanism that increases the severity of asthma in pregnancy.[24] These above findings suggest that maternal inflammatory factors associated with asthma may result in changes to placental function, with implications for fetal growth and development.[25,26]

The 11β-HSD2 activity difference was not observed where the fetus was male. There have been other reports of a sexual dimorphic response depending on whether the fetus is male or female.[27–30] Several reports have demonstrated a worsening of maternal asthma where the fetus is female,[14,15,] and a reduced growth in female fetuses[16] whereas where there is a male fetus an increase in stillbirths has been reported.[14,29] Proteomic studies of maternal and cord-blood in women with asthma have confirmed protein changes that correlate to asthma.[31] Subsequently 65 genes were found to be altered in the placentae from women whose pregnancy was complicated by asthma compared with normal non-asthmatic pregnancies. Of these only six genes were altered in male placentae. Fifty-nine gene changes were found in female placentae of the asthmatic mothers and these genes included genes associated with growth, inflammation and immune pathways.[32]

The effect of asthma on pregnancy outcomes

Asthma is an inflammatory disease of the airways and it has been proposed that inflammatory factors from the mother may have an impact on placental function and fetal development.[25,33] While there are few data elucidating the potential mechanisms of such an effect there is substantial evidence that pregnant women with asthma are at increased risk of poor perinatal outcomes, including reduced fetal growth, pre-eclampsia and preterm birth. The literature has been conflicting on this issue, due to substantial variations in study design, sample size and adjustment for confounders, with the larger database studies often indicating an increased risk of poor outcomes. A recent systematic review and meta-analysis indicates that there are significantly increased moderate risks of poor perinatal outcomes in pregnant women with asthma compared to pregnant women without asthma (Table 1).[34] This review also highlighted that some adverse perinatal outcomes (particularly preterm labour and delivery) may be improved by active asthma management, suggesting that prevention of exacerbations, maternal hypoxia or inflammation may be useful in improving pregnancy outcomes. The relative risk of low birthweight among asthmatic women was found to be 1.46 (95% confidence interval 1.22, 1.75) compared to women without asthma. Previous analyses indicated that women with severe asthma exacerbations during pregnancy were at 2.54 times the risk of low birth weight (95% CI 1.52, 4.25) compared to asthmatic women during pregnancy.[15] Together these data indicate that exacerbations of asthma are an important component that specifically increases the risk of adverse perinatal outcomes. It is possible that asthma severity is also important. Women with more severe asthma are at increased risk of asthma exacerbations in pregnancy[14,15] and have been shown to have poorer perinatal outcomes. There is evidence that exacerbations, oral steroid use and severe asthma are associated with preterm delivery, possibly due to maternal hypoxia, the effects of maternal inflammation, and/or changes in uterine smooth muscle function. Schatz et al. found a significant relationship between reduced lung function and preterm delivery, suggesting that severe asthma is a risk factor.[35] Reduced lung function may also be a marker of poor control of asthma, which influences preterm delivery via hypoxic mechanisms.[35] The release of inflammatory mediators from the mother as a result of asthma may also be involved[33] given the association between other active inflammatory diseases such as rheumatoid arthritis and low birth weight or preterm delivery.[36,37] There is however, no recent evidence available about the relationship between hypoxic episodes due to asthma and perinatal outcomes.

Others have highlighted the increase in psychological morbidity for pregnant asthmatics, specifically depression.[38,39] Thus it can be seen that asthma in pregnancy is not a benign condition and can have significant bearing on a range of perinatal outcomes. Perhaps more significantly as asthma is clearly treatable and manageable with long term treatment, obstetricians can not only affect outcomes related to asthma directly but also perhaps have an effect on some of the common perinatal outcomes such as those listed in Table 1. Therefore there is a need for appropriately designed studies

Table 1 **Perinatal outcome and relationship to maternal asthma[34]**

Perinatal outcome	Relative risk compared to women without asthma	95% Confidence interval	Number of studies	Number of women studied
Low birth weight	1.46	1.22–1.75	11	1,109,907
Small for gestational age	1.22	1.14–1.31	11	1,083,861
Preterm delivery	1.41	1.23–1.62	15	988,852
Pre-eclampsia	1.54	1.32–1.81	14	1,178,958

to test the impact of appropriate treatment of asthma in pregnancy on perinatal outcomes.

Pulmonary function in pregnancy

In normal pregnancy there is an increase in oxygen consumption of 20% with an increased maternal metabolic rate of 15%.[5] The functional residual capacity (amount of air remaining in the lungs during normal breathing) decreases by 17–20%; the residual volume (air remaining in the lungs after maximal expiration) decreases by 20–25%; the tidal volume (air displaced between inhalation and exhalation with no extra effort) increases by 30–50%; the expiratory reserve volume (the air that can be further pushed out at the end of normal expiration) decreases by 5–15%; and the minute volume/ventilation (volume of air inhaled or exhaled in 1 minute) increases by 30–50%. The respiratory rate, FEV_1 and peak expiratory flow rate (PEF) are unchanged. This makes the latter two very suitable methods for assessing pulmonary function in pregnancy. The changed minute ventilation and increased tidal volume results in a relative hyperventilation with a subsequent respiratory alkalosis (pH of 7.40 to 7.45; PCO_2 of 28 to 32 mmHg) compensated for by renal excretion of bicarbonate. There is a mild increase in maternal arterial PO_2 (106–110 mmHg) with the umbilical venous PO_2 being lower than that of the placental venous channels. As such any maternal hypoxia quickly results in substantial fetal hypoxia. Coleman and Rund reported that a PO_2 of 60 causes fetal jeopardy.[40] The length of the hypoxia would relate to the degree of fetal compromise.

Assessment of respiratory function in pregnancy

The measurement of FEV_1 with spirometry is often recommended for the assessment of pulmonary function during pregnancy. However, if the required equipment is not readily accessible, the measurement of PEF with a hand-held peak flow meter can be easily managed in the clinic or home situation.[5] Spirometry and PEF readings can then be used to initially assess the pulmonary function in a woman who gives a history of asthma and can subsequently be used as a baseline value throughout the pregnancy to assess the response to therapy should that be needed to detect deterioration.

The measurement of exhaled nitric oxide has been proposed as a method for the assessment of airway inflammation or oxidant stress in asthma.[41] Recently this methodology has been evaluated for the assessment of severity and control of asthma in pregnancy with the aim of achieving personalised management.[42] A double-blinded randomised controlled trial of asthma therapy guided by fraction of exhaled nitric oxide (F_ENO) versus standard spirometry and symptom assessment has now been completed.[43] The Management of Asthma in Pregnancy (MAP) trial used F_ENO to assist with relating drug therapy to clinically measured responses. Like spirometry, F_ENO is unchanged in pregnancy. The nitric oxide synthase (NOS) isoform, inducible NOS (iNOS) is constitutively expressed by airway epithelium and is up-regulated by inflammatory mediators. It is the major determinant of NO concentration in exhaled breath. Accompanying this is increased diffusibility of NO in the asthmatic airway. As such, F_ENO correlates well with measures of eosinophilic airway inflammation.[44]

Women who were non-smokers with a doctor's diagnosis of asthma and were using inhaled corticosteroid therapy (ICS) within the last year were recruited at 12–20 weeks pregnancy. Evaluations consisted of F_ENO, spirometry, the asthma control questionnaire (ACQ) and quality-of-life questionnaires. The ACQ is a useful and validated 7-item questionnaire that assesses control of asthma and can be used to monitor disease activity over time. The ICS therapy was a budesonide turbuhaler. Randomization was to a clinical guideline algorithm (control group) or a F_ENO algorithm to adjust therapy (active intervention group). The F_ENO algorithm was a sequential process with F_ENO used to adjust the dose of ICS (with 15ppb being the cut off for reduction or increase) and ACQ score (with 1.5 used as the cut-off point) used to adjust the dose of long-acting $beta_2$ -agonist. The study showed improved management with F_ENO with decreased asthma exacerbations (0.56 to 0.26, $P = 0.002$), decreased oral corticosteroid use ($P = 0.042$), decreased $beta_2$ -agonist use in the previous week (1 to 0, $P = 0.024$), with increased ICS use (42.2% to 68.5%, $P<0.0001$) but with a decrease in the mean daily ICS dose ($P = 0.043$) and increased long-acting beta-$_2$ agonist use (17.4% to 40.5%, $P<0.0001$). The mean ACQ were lower in the F_ENO group ($P = 0.046$) and the neonatal intensive care hospitalisation was lower ($P = 0.046$). The number needed to treat was 6. A similar study powered to assess any changes in perinatal outcomes namely preterm delivery and low birthweights is planned.

Treatment of asthma in pregnancy

The current approach to management seeks to achieve optimal disease control, which means using medication and other management strategies to achieve minimal symptoms (ideally none) of asthma, optimal lung function, and to reduce the future risks of asthma exacerbations.[45] The approach uses a step-wise increase in medication intensity with a step-wise reduction in pharmacotherapy once the asthma comes under control, using the same step-wise approach in reverse. The benefits of this approach are good symptom control in the majority of patients, improved quality of life, and significantly reduced exacerbation risk.[46] This is of particular importance in pregnancy since women with asthma experience a high rate of asthma exacerbations, and these impact adversely on both mother and fetus.[8,14,15,34]

The mainstay of successful management is team work with the ultimate goal to eliminate if possible maternal episodes of hypoxia[5] ensuring that asthma control is optimal and that this treatment is maintained throughout pregnancy.[47] It is clear from multiple observers that there is a definite trend for both undertreatment and cessation of optimal treatment for many women who have a history of asthma and are pregnant.[8,21,39] The causes of this undertreatment appear to be two-fold. Namely there are concerns amongst women and their healthcare providers regarding the effects of asthma medications on the developing fetus and as described above a lack of understanding regarding management of asthma in pregnancy by the obstetric or emergency department team.[42,48,49] The concerns of the women need to be addressed regarding any possible danger to their fetus. There are now large numbers of data that support the safety of current drugs used for the management of asthma and these are reviewed below.[50]

Beta$_2$-agonists

Animal and human studies (6,667 pregnant women) show reassuring data for short-acting beta$_2$-agonists but there is less information regarding long-acting beta$_2$-agonists (LABA).[51] In pregnancy, LABA are considered for use in moderate-severe asthma, in combination with ICS therapy. Few studies have examined their safety in this context, most being post-marketing surveillance studies or small cohort or case-control studies examining congenital malformations. One study reported no adverse outcomes among 65 pregnant women who used salmeterol.[52] A recent study from Quebec, found no significantly increased odds of any or major malformations with first trimester LABA use (adjusted OR 1.37, 95% CI 0.92, 2.17 for any malformations).[53] There was an increased risk of major cardiac malformations (adjusted OR 2.38, 95% CI [1.11, 5.10]) among asthmatic users of LABA compared to non-users of LABA. The 165 women in this cohort who used LABA were more likely to have asthma exacerbations, more likely to use high doses of ICS and more likely to use oral corticosteroids (OCS) during pregnancy, meaning that there was the possibility of residual confounding by asthma severity. Based on a longer period of availability, 2004 guidelines recommended salmeterol as the preferred LABA used in pregnancy.[50]

Theophylline

Data from 57,163 pregnant women were reported. Theophylline was as effective as beclomethasone diproprianate but was associated with a higher side effect rate and higher discontinuation rates.[54] Theophylline is rarely used outside of the USA and the developing world.

Inhaled corticosteroids (ICS)

Results from studies on 21,072 pregnant women were reported with three major conclusions from review of the evidence: (1) The risk of asthma exacerbations in pregnancy were reduced with improved lung function (FEV_1). (2) There are no data showing any increase in congenital malformations or adverse perinatal outcomes. (3) The majority of experience with ICS to date is with budesonide.

Only one study from Sweden showed a weak increase in congenital malformations (OR 1.09, 95% CI = 1.03–1.15) but concluded that the differences could be a random occurrence.[51]

Further support for the use of steroids is seen in placental studies which have shown a vasodilatory effect on placental vasculature in an in-vitro model[55] and that assessment of fetal glucorticoid-regulated pathways (i.e. fetal adrenal function) shows no effect from ICS therapy on fetal adrenal function.[56,57]

Oral (systemic) corticosteroids

Data are available from studies of 52,038 pregnant women with 238 having taken oral corticosteroids. During the first trimester there is a slight increased risk of isolated cleft lip, with or without cleft palate, (0.3% versus 0.1%). There are also associations with preterm delivery, low birthweight and preeclampsia.[58] It is however, difficult to delineate what is an attributable effect from the corticosteroids versus the effects of severe or uncontrolled asthma. However, similar results are seen when oral corticosteroids are used for other indications.

Sodium cromoglycate

The use of inhaled sodium cromoglycate in pregnancy is supported by data from 4,110 pregnant women demonstrating no specific adverse effects.

Leukotriene modifiers

The numbers of women taking these agents (notably montelukast and zafirlukast) are small with minimal data available.[59]

Summary

The overwhelming message is that asthma therapies are generally considered low risk in pregnancy. All standard asthma therapies may be used in pregnancy but sodium cromoglycate, leukotriene receptor antagonists and theophylline are less preferred. Although the evidence on LABA safety is lacking, it is recommended for use in combination with ICS for moderate-severe asthma.

The aims of management of these women is providing optimal therapy to avoid exacerbations, maintain maternal health and optimise fetal growth and maturation. It is far safer for these women to be treated with medications than to suffer asthma symptoms and exacerbations. As such it is important for the obstetrical carers to be aware of the woman's asthma status at each antenatal visit. Aspects of standard asthma management include:[50,60]

(1) Monthly assessment including measuring pulmonary function with PEF following initial spirometry as recommended in the guidelines.
(2) Control and avoidance of triggering factors such as allergens, irritants and smoking.
(3) Ensure appropriate seasonal immunisations including influenza and pertussis.
(4) Patient education including an asthma plan for exacerbations, self-monitoring and correct use of inhalers.
(5) Asthma control is assessed at each antenatal visit, for example, using the asthma control questionnaire and current asthma medication is reviewed. When asthma is not controlled a step-wise approach to pharmacological therapies[45,61–63] involving increasing therapeutic interventions from intermittent short-acting beta$_2$-agonists as needed; then the addition of daily low-dose ICS; then either a combination of low-dose ICS and long-acting beta$_2$-agonist, or increasing dose of ICS to medium-dose range, increased to high-dose range; addition of systemic corticosteroid if needed.
(6) Acute exacerbations can be managed according to the asthma plan either at home, emergency department or hospital depending on the severity. Guidelines for asthma management in pregnancy indicate that when a patient has a PEF <50% of predicted for personal best, marked wheezing or shortness or breath, or is noticing decreased fetal activity (with other causes excluded), then oral steroids should be added, short acting beta agonists given repeatedly, and the patient should proceed to the

Table 2 **Classification of asthma severity and control in pregnant women**[68]

Asthma severity	Symptom frequency	Night-time awakening	Interference with normal activity	FEV_1 or peak flow (Predicted % of personal best)
Well controlled	≤ 2 days /week	≤ 2/month	None	>80%
Mild	>2/week, not daily	>2/month	Minor	>80%
Moderate	Daily	>1/week	Some limitation	60–80%
Severe	Throughout day	4/week	Extreme limitation	<60%

FEV_1, forced expiratory volume in the first second of expiration

emergency department for further management.[50] (See Table 2.)

(7) As rhinitis, sinusitis and gastroesophageal reflux disease (GERD) are often associated with asthma they will need managing with intranasal corticosteroids and or antihistamines (for rhinitis and sinusitis) and proton-pump inhibitors (for GERD). Intranasal steroids have been suggested as the optimal management for allergic rhinitis.[64,65] However, trials of proton-pump inhibitors in symptomatic asthmatics with asymptomatic GERD have not shown improvement in terms of pulmonary function or asthma symptomatology.[66]

Obstetric management

Women with asthma should have an agreed asthma management plan. First trimester ultrasound to accurately date the pregnancy is advised. If the asthma is stable and well controlled then a standard pattern of antenatal care and visit schedule can be maintained and at each visit the status of the asthma should be assessed. However, for moderate or severe asthma in pregnancy increased visits and surveillance will be necessary. The increased surveillance will entail ultrasound to assess fetal growth and Doppler ultrasound assessment of the fetal umbilical placental circulation. Further assessment will involve fetal heart rate monitoring, cardiotocography (CTG), usually commencing at 32 weeks or earlier if the severity of the asthma indicates possible fetal compromise. In the presence of an acute exacerbation, early and adequate intervention is needed:[67–70]

- Close monitoring and assessment of fetal wellbeing (ultrasound and CTG)
- Maintain oxygen saturation >95%
- Avoid $PaCO_2$ >40mm Hg
- Position the woman in the left lateral position
- Maintain hydration and avoid hypotension
- Consider intubation earlier than usual by an experienced obstetric anaesthetist

In labour continue with asthma medications if they are required. If the woman has used systemic hydrocortisone, give 100 mgs 8th hourly during labour, maintain hydration, favour lumbar epidural analgesia and avoid bronchoconstricting agents (prostaglandin $F_{2\alpha}$). Prostaglandin E_1 or E_2 can be used. Caesarean section delivery is usually indicated on obstetric grounds rather than asthma-related indications. Post-partum there are no contraindications to the continuation of asthma therapy and breastfeeding.[50]

CONCLUSIONS

All clinicians managing women with asthma in pregnancy need to be aware of the significance of this problem with respect to the following:

(1) Asthma that is not controlled is associated with worse perinatal outcomes.
(2) The aim of management is the provision of optimal therapy to maintain maternal health and normal fetal growth and maturation. It is far safer for these women to be treated with medications than to suffer asthma symptoms and exacerbations.
(3) The mainstays of therapy are $beta_2$-agonists and ICS.
(4) Management plans involve regular assessment of asthma control and institution of step-wise introduction and increases of therapies.
(5) Currently monitoring of asthma in these women is with peak flow meters. Future developments may indicate that F_ENO may be the method of choice.
(6) Fetal monitoring is guided by the level of asthma control, with women with moderate or more severe asthma needing ultrasound and CTG assessment of the fetus.

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